AMENDMENTS TO THE SPECIFICATION

Applicant respectfully requests that the specification be amended as follows.

Please replace the first paragraph of Section 3.1 (page 5, beginning "As used herein, the term "cyclic AMP responsive element...") with the following paragraph:

As used herein, the term "cyclic AMP responsive element" or "CRE" refers to enhancer sequences which mediate signal transduction involving cAMP by interacting with transcription factors and/or associated proteins of the transcriptional complex. These sequences (some which bind to cAMP) include, but are not limited to, non-native sequences, consensus sequences (e.g., 5'-TGACGTCA-3'), as well as CREs, CRE-like sequences, and putative CREs that are associated with native genes. These sequences may comprise, for example, TTACGTCA (Short et al., 1986, "Characterization of the phosphoenolpyruvate carboxykinase (GTP) promoter-regulatory region. II. Identification of cAMP and. glucocorticoid regulatory domains", J. Biol. Chem. 261:9721), TGACGTCT (Tsukada et al., 1987, "Identification of a region in the human vasoactive intestinal polypeptide gene responsible for regulation by cyclic AMP", J. Biol. Chem. 262:8743), TGACGTAG (VanBeveren et al., 1983, "Analysis of FBJ-MuSV provirus and c-fos (mouse) gene reveals that viral and cellular fos gene products have different carboxy termini", Cell 32:1241), CTGCGTCA (Comb et al., 1986, Nature 323:353), TGACGTCA (Mahata et al., 1996, "Dispersion of chromogranin/secretogranin secretory protein family loci in mammalian genomes", Genomics 33(1):135-9), TGCGTCAGC (X59520; Vitale et al., 1991, "Molecular cloning of the mouse CCK gene: expression in different brain regions and during cortical development", Nucleic Acids Res. 19(1): 169-77), TGACG, CGTCA (D34613; Yokoyama et al., 1991, "Molecular cloning of human platelet thromboxane A synthase", Biochem Biophys Res Comm. 178(3):1479-84), TGACATCA (D28873; Ogawa et al., 1994, "Molecular cloning and chromosomal assignment of the mouse C-type natriuretic peptide (CNP) gene (Nppc): comparison with the human CNP gene (NPPC)" Genomics 24(2):383-7), GTCGTCA, TCGTCAC (D28235; Hla and Neilson, 1992 "Human cyclooxygenase-2 cDNA", Proc Natl Acad Sci USA 89(l6):7384-8), TCCCAGGC (AF)22742; Yao et al., 1999, "Molecular cloning and sequence analysis of the 5 -flanking 5 region of the Sprague-Dawley rat thrombomodulin gene", DNA Seq. 10(1): 55-60), (D16641, D28874; Ogawa et al., 1995, "Characterization of the

5'-flanking region and chromosomal assignment of the human brain natriuretic peptide gene", J Mol Med. 73(9):457-63; a nucleotide sequence comprising -161 to -152 of the glucose-6-phosphatase hydrolytic subunit gene promoter (AF051355; Schmoll et al., 1999, "Identification of a cAMP response element within the glucose-6-phosphatase hydrolytic subunit gene promoter which is involved in the transcriptional regulation by cAMP and glucocorticoids in H4IIE hepatoma cells", Biochem J. 338 (Pt 2):457-63), TGACGTG (AF061881; Sarabia and Liehr, 1999, "Differential regulation of c-fos expression in estrogen-induced hamster renal tumors compared with kidney not due to creation of an estrogen-response element by point mutation in the genes flanking sequence", Mol Carcinog. 24(4):255-62), CTGACGTCA (AF023677; Hardy SH, Walker SJ, Goodman RL and Vrana KE), sequences comprising a portion (e.g., at least 5, 6, 7, 8,9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 consecutive nucleotides) of TTCAGCAAAAATGTCGACATATCTTCCACACCCCCCTGGTTCTGACCTCTCAGCAAG GCATTTGGCTTTGAAAGGCCGTTTTGT (SEQ ID NO:30; D50689; Izuhara et al., 1995, "Transcription of the rat liver uricase-encoding gene is regulated via a cis-acting element responsive to cAMP", Gene. 167(1-2):267-72), TGACCTCA (M89636; Zhu et al., 1992, "Promoter organization and activity of human monoamine oxidase (MAO) A and B genes", J Neurosci. 12(11):4437-46), a nucleotide sequence comprising -306 to -289 of the Dictyostelium gp80 gene (X66483, S45379; Desbarats et al., 1992, "Identification of a unique cAMP-response element in the gene encoding the cell adhesion molecule gp80 in Dictyostelium discoideum", J Biol Chem. 267(27): 19655-64), TGAGCTCA, sequences comprising a portion of (e.g., at least 5, 7, 10, 14, 16, 18 or 20 consecutive nucleotides) GACCGCATTTTCAAAAAGCTGCTCTGAGAGTAGATGACGTAAATAAAGCCCTTGTAA CAG[[,]] TGACGTA (SEQ ID NO:31; X17367; Sensel et al., 1990, "Isolation and characterization of clones for the rat hepatic lipase gene upstream regulatory region" Biochim Biophys Acta. 1048:297-302), CGTCA (X74961; Virkkunen et al., 1994, "Structural comparison of human and rat prostate-specific acid phosphatase genes and their promoters: identification of putative androgen response elements", Biochem Biophys Res Commun. 202(1):49-57), TGACGTCC (X13257; Kobayashi K., Kurosawa Y., Fujita K, Nagatsu T., 1989, "Human dopamine beta-hydroxylase gene: two mRNA types having different 3-terminal regions are produced through alternative polyadenylation.", Nuc Acids Res. 17(3):1089-1102),

CTGACATCAC (SEQ ID NO:24, Freeland et al., 1988, "Nucleotide sequence of the region upstream of the rat growth hormone gene") (Xl2967; Thomas et al., 1990, "Z-DNA formation in the rat growth hormone gene promoter region", Mol Cell Biol. 10(10):5378-87), AGACGTCA (X57155; Sanders L, McLane MW and Schatteman GC; Perez-Albuerne et al., 1993, "Transcriptional regulatory elements downstream of the JunB gene", Proc Natl Acad Sci USA 90(24):11960-4), TGACATCA, CTGACACCAG (SEQ ID NO:25) (M23565; Miller et al., 1988, "Structure of a gap junction gene: rat connexin-32", Biosci Rep. 8(5):455-64), TGACGTCA, TGACGTGT (U24128; Jansen et al., 1995, "Neuroendocrine-specific expression of the human prohormone convertase 1 gene: Hormonal regulation of transcription through distinct cAMP response elements", J Biol Chem. 270(25):15391-7), TCACGTCAC (J04154; Changelian et al., 1989, "Structure of the NGFI-A gene and detection of upstream sequences responsible for its transcriptional induction by nerve growth factor", Proc Natl Acad Sci USA 86(l):377-8 1), a nucleotide sequence comprising a portion of CCCTTCACCCACCTAGCTCTGTCCCGCAG (SEQ ID NO:32; M26440; Burt et at, 1989, "Identification of negative and positive regulatory elements in the human renin gene", J Biol Chem. 264(13):7357-62),. and TTCGTCA (M35425, J05432; Ameis et al., 1990, "Isolation and characterization of the human hepatic lipase gene", J Biol Chem. 265(12):6552-6555). Moreover, these sequences encompass variants of known CRE sequences, resulting from e.g., base substitution(s), addition(s) or deletion(s), and derivatives or analogues thereof. Each of the above references is incorporated herein by reference in its entirety.

Please replace the paragraph beginning at page 12, line 16 ("In one embodiment, the bcl-2 antisense sequence...") with the following paragraph:

In one embodiment, the bcl-2 antisense sequence comprises at least 10 bases or at least 10 consecutive bases that are complementary to a bcl-2 pre-mRNA or bcl-2 mRNA. In one embodiment, the bcl-2antisenseoligomer is 10, 11, 12,13,14,15,16,17,18,19,20, 21, 22, 23, 24, or 25 bases in length. In another embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCG-3' (SEQ ID NO:35). In another embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCGT-3' (SEQ ID NO:41). In another embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCGTG-3' (SEQ ID NO:44). In

another embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCGTGC-3' (SEQ ID NO:45). In another embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCGTGCG-3' (SEQ ID NO:46:). In another embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCGTGCGC-3' (SEQ ID NO:47). In another embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCGTGCGCC-3' (SEQ ID NO:48). In yet another embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCGTGCGCCA-3' (SEQ ID NO:49). In another embodiment, the bcl-2 oligomer comprises the sequence: 5'-TCTCCCAGCGTGCGCCAT-3' (SEQ ID NO:17; also known as G3139 or Genasense™). In other embodiments, the bcl-2 oligomer comprises CAGCGTGCGCCATCCTTCCC (SEQ ID NO: 1), CTTTTCCTCTGGGAAGGATGGCGCACGCTGGGAGA (SEQ ID NO :2), GATGCACCTACCCAGCCTCC (SEQ ID NO:3), ACGGGGTACGGAGGCTGGGTAGGTGCATCTGGT (SEQ II) NO:4), ACAAAGGCATCCTGCAGTTG (SEQ ID NO:5), CCCCCAACTGCAGGATGCCTTTGTGGAACTGTACGG (SEQ ID NO:6), GGGAAGGATGGCGCACGCTG (SEQ ID NO:7), CGCGTGCGACCCTCTTG (SEQ ID NO:8), TACCGCGTGCGACCCTC (SEQ ID NO:9), TCCTACCGCGTGCGACC (SEQ ID NO:10), CCTTCCTACCGCGTGCG (SEQ ID NO:11), GACCCTTCCTACCGCGT (SEQ ID NO: 12), GGAGACCCTFCCTACCG (SEQ ID NO: 13), GCGGCGGCAGCGCGG (SEQ ID NO:14), CGGCGGGGCGACGGA (SEQ ID NO: 15), CGGGAGCGCGGCGGGC (SEQ ID NO:[[15]]16), TCTCCCAGCGTGCGCCAT (SEQ ID NO:[[16]]17), TGCACTCACGCTCGGCCT (SEQ ID NO:[[17]]18), ~~TCTCCCAGCGTGCGCCAT (SEQ ID NO:24), TGCACTCACGCTCGGCCT (SEQ ID NO:25),~~ GCGCGGCGGGCGGGCGGGCA (SEQ ID NO:26), GGGCGGAGGCCGGCCGGCGG (SEQ ID NO:27), AGCGGCGGCGGCGGCAGCGC (SEQ ID NO:28), or GGGCCGGGAAGGGCGCCCGC (SEQ ID NO:29), which correspond to SEQ ID NOS. 1 to 18 and 24 to 29, respectively, in U.S. Patent No. 5,831,066 which is incorporated herein by reference in its entirety.

Please replace the paragraph beginning at page 22, line 13 ("Bcl-2 antisense sequences suitable for use...") with the following paragraph:

Bcl-2 antisense sequences suitable for use in a bcl-2/CRE hybrid oligomer include oligomers which range in size from 5 to 9, 10 to19, 20 to 49, 50 to 74, 75 to 100, or 101 to 1000 bases in length; preferably 10 to 40 bases in length; more preferably 15 to 25 bases in length;

most preferably 18 bases in length. In one embodiment, the bcl-2 antisense oligomer is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 bases in length. In one embodiment, the bcl-2 antisense sequence comprises at least 10 bases that are complementary to the bcl-2 pre-mRNA or mRNA. In a further embodiment, the bcl-2 antisense sequence comprises at least 10 consecutive bases that are complementary to the bcl-2 pre-mRNA or mRNA. In one specific embodiment, the bcl-2 oligomer comprises the sequence 5'-TCTCCCAGCG-3' (SEQ ID NO:35). In another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-CGTGCGCCAT-3' (SEQ ID NO:50). In another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-CCAGCGTG-3'. In another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-CCAGCGTGC-3'. In another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-CCAGCGTGCG-3' (SEQ ID NO:51). In another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-CCCAGCGTGCGC-3' (SEQ ID NO:52). In another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-TCCCAGCGTGCGCC-3' (SEQ ID NO:53). In another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-CTCCCAGCGTGCGCCA-3' (SEQ ID NO:54). In yet another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-TCTCCCAGCGTGCGCCAT-3' (SEQ ID NO:17; also known as G3139).

Please replace the paragraph beginning page 26, line 28 ("In another embodiment, the hybrid oligomer comprises...") with the following paragraph:

In another embodiment, the hybrid oligomer comprises a CRE oligomer comprising the CRE consensus sequence, TGACGTCA, at least two of which are linked by a nucleotide sequence comprising a bcl-2 antisense sequence (Table 1, construct 2b). In a further embodiment, the bcl-2 antisense sequence comprises at least 10 bases that are complementary to a bcl-2 pre-mRNA or mRNA. In a particular embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCGTGCGCCAT-3' (SEQ ID NO: 17). In another particular embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCGTGCGCCA-3' (SEQ ID NO:49). In another particular embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCGTGCGCC-3' (SEQ ID NO:48). In another particular embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCGTGCGC-3' (SEQ ID NO:47). In

another particular embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCGTGCG-3' (SEQ ID NO:35). In another particular embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCGTGC-3' (SEQ ID NO:45). In another particular embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCGTG-3' (SEQ ID NO:44). In another particular embodiment the bcl-2 antisense sequence comprises the sequence 5'-CTCCCAGCGT-3' (SEQ ID NO:55). In yet another particular embodiment, the bcl-2 antisense sequence comprises the sequence 5'-TCTCCCAGCG-3' (SEQ ID NO:56). In a specific embodiment, the hybrid oligomer comprises the sequence 5'-TGACGTCATCTCCCAGCGTGCGCC-3' (SEQ ID NO:57). In another specific embodiment, the phosphorothioate hybrid oligomer comprises the sequence 5'-TGACGTCATCTCCCAGCGTGCGCCATTGACGTCA-3' (SEQ ID NO:[[17]]33).

Please replace the paragraph beginning at page 32, line 34 ("In one embodiment, the bcl-2 antisense oligomer comprises...") with the following paragraph:

In one embodiment, the bcl-2 antisense oligomer comprises a sequence of which at least 10 bases, optionally consecutive, are complementary to the bcl-2 pre-mRNA or mRNA. In one specific embodiment, the bcl-2 oligomer comprises the sequence 5'-TCTCCCAGCG-3' (SEQ ID NO:35). In another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-CGTGCGCCAT-3'(SEQ ID NO:50). In another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-CCAGCGTGCG-3' (SEQ ID NO:51). In another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-CCCAGCGTGCGC-3' (SEQ ID NO:52). In another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-TCCCAGCGTGCGCC-3' (SEQ ID NO:53). In another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-CTCCCAGCGTGCGCCA-3' (SEQ ID NO:54). In yet another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-TCTCCCAGCGTGCGCCAT-3' (SEQ ID NO:17; also known as G3139).

Please replace the paragraph beginning at page 33, line 24 ("In a specific embodiment, an 18-base phosphorothioate...") with the following paragraph:

In a specific embodiment, an 18-base phosphorothioate bcl-2 antisense oligomer of the sequence 5'-TCTCCCAGCGTGCGCCAT-3' (SEQ ID NO:17), which is complementary to the first six codons of the bcl-2 mRNA and hybridizes to the respective target RNA bases, is administered in combination with a 24-base phosphorothioate CRE decoy of the sequence 5'-TGACGTCATGACGTCATGACGTCA-3' (SEQ ID NO:36).

Please replace the paragraph beginning at page 40, line 26 ("In a specific embodiment, the phosphorothioate hybrid...") with the following paragraph:

In a specific embodiment, the phosphorothioate hybrid oligomer of the sequence 5'-TGACGTCATCTCCCAGCGTGCGCCATTGACGTCA-3' (SEQ ID NO:33) is administered for a short treatment cycle, defined as a period of less than two weeks.

Please replace the paragraph beginning at page 56, line 3 ("The invention further provides a pharmaceutical kit...") with the following paragraph:

The invention further provides a pharmaceutical kit comprising an effective amount of a bcl-2/CRE hybrid oligomer, CRE decoy oligomer and/or bcl-2 antisense oligomer, in combination with a cancer therapeutic agent, to protect from or treat a cell-proliferative related disorder. In one embodiment, an effective amount of a bcl-2/CRE hybrid oligomer, CRE decoy oligomer, and/or bcl-2 antisense oligomer, and a pharmaceutically acceptable carrier, are packaged in a single dose vial or other container. In a particular embodiment, an effective amount of one or more CRE decoy oligomers and one or more bcl-2 antisense oligomers and a pharmaceutically acceptable carrier, are packaged in a single dose vial or other container. In a specific embodiment, the bcl-2 oligomer comprises the sequence 5'-TCTCCCAGCGTGCGCCAT-3' (SEQ ID NO:17), and the CRE decoy oligomer comprises the sequence 5'-TGACGTCATGACGTCATGACGTCA-3' (SEQ ID NO:36). In another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-TCTCCCAGCGTGCGCCAT-3' (SEQ ID NO:17), and the CRE decoy oligomer comprises the sequence 5'-TGACGTCATTTTTTGACGTCA-3' (SEQ ID NO:37). In another specific embodiment, the bcl-

2 oligomer comprises the sequence 5'-TCTCCCAGCGTGCGCCAT-3' (SEQ ID NO:17), and the CRE decoy oligomer comprises the sequence 5-TGACGTCATTGACGTCA-3' (SEQ ID NO:38). In another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-TCTCCCAGCGTGCGCCAT-3' (SEQ ID NO:17), and the CRE decoy oligomer comprises the sequence 5'-TGACGTCATTTGACGTCA-3' (SEQ ID NO:39). In yet another specific embodiment, the bcl-2 oligomer comprises the sequence 5'-TCTCCCAGCGTGCGCCAT-3' (SEQ ID NO: 17), and the CRE decoy oligomer comprises the sequence 5'-GACGTCATTGACGTCA-3' (SEQ ID NO:40). The kit may comprise one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Please replace Table 1, at page 58, with the following Table 1. Applicant notes that the underlining in the BK1-PS sequence is not inserted text, but was present in Table 1 as originally presented:

Table 1

BK1-PS (phosphorothioate DNA) (SEQ ID NO:[[35]]33) 5' tga cgt cat **ctc cca gcg tgc gcc att** gac gtc a 3' (complementary arms are underlined, bcl-2 complement is in **bold**)	34-mer
BK2-PS (phosphorothioate DNA) 5'tga cgt cat gac gtc atg acg tca 3' (SEQ ID NO:36)	24-mer
BK3-PS (phosphorothioate DNA) 5' tga cgt cat ttt tga cgt ca 3' (SEQ ID NO:37)	20-mer
BK4-PS (phosphorothioate DNA) 5' tga cgt cat ttt gac gtc a3' (SEQ IDNO:38)	19-mer
BK5-PS (phosphorothioate DNA) 5' tga cgt cat tt gac gtc a 3' (SEQ ID NO:39)	18-mer
BK6-PS (phosphorothioate DNA) 5' tga cgt cat tga cgt ca 3' (SEQ ID NO:40)	17-mer

BK7-DE (all-phosphodiester DNA) (SEQ ID NO:[[41]]33) 5' tga cgt cat ctc cca gcg tgc gcc att gac gtc a 3' 34-mer
1084 RNA Target (BCL2 RNA target region from -3 to +20) 5' agg atg gcg cac gct ggg aga ac 3' (SEQ ID NO:42) (G3139 complement is underlined)

Please replace Table 2 at page 59 with the following Table 2. Applicant notes that the underlining appearing in the BK1-PS+1084 and BK7-DE+1084 sequences is not inserted text, but was present in Table 2 as originally presented:

Table 2

Name	Oligonucleotide Sequence 5'-3' (Target RNA 3'-5', RNA/DNA duplex underlined)	T_m ave. ramp up	T_m ave. ramp down	T_m °C Ave±SD
BK1-PS	tga cgt cat ctc cca gcg tgc gcc att gac gtc a (SEQ ID NO:33)	51.1	46.2	48.7±0.9
BK2-PS	tga cgt cat gac gtc atg acg tca (SEQ ID NO:36)	60.8	58.4	59.6
BK3-PS	tga cgt cat ttt tga cgt ca (SEQ ID NO:37)	64.3	60.3	62.3
BK4-PS	tga cgt cat ttt gac gtc a (SEQ ID NO:38)	62.8	61.7	62.3
BK5-PS	tga cgt cat ttg acg tca (SEQ ID NO:39)	63.5	60.1	61.8±1.3
BK6-PS	tga cgt cat tga cgt ca (SEQ ID NO:40)	61.6	62.4	62.0
BK7-PS	tga cgt cat ctc cca gcg tgc gcc att gac gtc a (SEQ ID NO:33)	63.4	60.4	61.9±0.9
BK1-PS +1084	tga cgt cat ctc cca gcg tgc gcc att gac gtc a (SEQ ID NO:[[43]]33) ca[[ac]]a gag ggt cgc acg cgg tag ga (SEQ ID NO:42)	3.7	72.4	73.1
BK7-DE +1084	tga cgt cat ctc cca gcg tgc gcc att gac gtc a (SEQ ID NO:33) ca[[ac]]a gag ggt cgc acg cgg tag ga (SEQ ID NO:42)	80.4	78.3	79.4